DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 21-752

Gilead Sciences, Inc.
Attention: Martine Kraus, Ph.D., Director, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Dr. Kraus:

Please refer to your new drug application (NDA) 21-752 dated March 11, 2004, received March 12, 2004, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Truvada™ (emtricitabine (200 mg) and tenofovir disoproxil fumarate (300 mg)) tablets.

We acknowledge receipt of your submissions dated April 5, 2004, May 11, 2004, May 23, 2004, May 28 (2), 2004, June 3, 2004 (2), June 8, 2004, June 9, 2004 (2), June 10, 2004, June 18, 2004 (2), June 23, 2004, July 7, 2004, July 9, 2004, July 12, 2004, July 14, 2004, July 17, 2004, July 19, 2004, July 21, 2004, July 23, 2004, July 27, 2004 (2), and July 28, 2004.

This new drug application provides for the use of Truvada™ (emtricitabine (200 mg) and tenofovir disoproxil fumarate (300 mg)) Tablets in combination with other antiretroviral agents (such as non-nucleoside reverse transcriptase inhibitors or protease inhibitors) for the treatment of HIV-1 infection in adults.

We completed our review of this application, as amended. It is approved under the provisions of the accelerated approval regulations (21 CFR 314.510), effective on the date of this letter, for use as recommended in the agreed-upon labeling text, required patient labeling and with minor editorial revisions summarized below and in the enclosed labeling. Marketing of this drug product and related activities must adhere to the substance and procedures of the referenced accelerated approval regulations.

Revisions for the Package Insert (PI):

In the MICROBIOLOGY, Mechanism of Action, *Emtricitabine* section, the paragraph should read:

"Emtricitabine: Emtricitabine, a synthetic nucleoside analog of cytidine, is phosphorylated by cellular enzymes to form emtricitabine 5'-triphosphate. Emtricitabine 5'-triphosphate inhibits the activity of the HIV-1 reverse transcriptase (RT) by competing with the natural substrate deoxycytidine 5'-triphosphate and by being incorporated into nascent viral DNA which results in chain termination. Emtricitabine 5'-triphosphate is a weak inhibitor of mammalian DNA polymerase α, β, ε and mitochondrial DNA polymerase γ."

In the MICROBIOLOGY, Resistance, *Emtricitabine and tenofovir disoproxil fumarate* section, the paragraph should read:

"Emtricitabine and tenofovir disoproxil fumarate: HIV-1 isolates with reduced susceptibility to the combination of emtricitabine and tenofovir have been selected in vitro. Genotypic analysis of these isolates identified the M184I/V and/or K65R amino acid substitutions in the viral RT."
In PRECAUTIONS, Drug Interactions, *Emtricitabine and tenofovir disoproxil fumarate* section, the second paragraph should read:

"TRUVADA is a fixed-dose combination of emtricitabine and tenofovir disoproxil fumarate. TRUVADA should not be co-administered with EMTRIVA or VIREAD. Due to similarities between emtricitabine and lamivudine, TRUVADA should not be co-administered with other drugs containing lamivudine, including COMBIVIR®, EPIVIR, EPIVIR-HBV®, EPZICOM™, or TRIZIVIR®."

In PRECAUTIONS, Information for Patients section, the seventh bullet point should read:

- "TRUVADA should not be co-administered with EMTRIVA or VIREAD, or drugs containing lamivudine, including COMBIVIR, EPIVIR, EPIVIR-HBV, EPZICOM, or TRIZIVIR."

The last paragraph of the PI should read:

"EMTRIVA, TRUVADA, and VIREAD are trademarks of Gilead Sciences, Inc. REYATAZ and VIDEX are trademarks of Bristol-Myers Squibb. COMBIVIR, EPIVIR, EPIVIR-HBV, EPZICOM and TRIZIVIR are trademarks of GlaxoSmithKline."

Revisions for the Patient Package Insert (PPI):

In the **Tell your healthcare provider about all the medicines you take** section, the first bullet point should read:

- "COMBIVIR®, EMTRIVA, EPIVIR®, EPIVIR-HBV®, EPZICOM™, TRIZIVIR®, or VIREAD. **TRUVADA should not be used with those medicines."**

In the **What should I avoid while taking TRUVADA?** section, the sixth bullet point should read:

- "COMBIVIR, EMTRIVA, EPIVIR, EPIVIR-HBV, EPZICOM, TRIZIVIR or VIREAD. **TRUVADA should not be used with these medicines."**

The last paragraph of the PPI should read:

"EMTRIVA, TRUVADA, and VIREAD are trademarks of Gilead Sciences, Inc. REYATAZ is a trademark of Bristol-Myers Squibb. COMBIVIR, EPIVIR, EPIVIR-HBV, EPZICOM and TRIZIVIR are trademarks of GlaxoSmithKline."

The final printed labeling (FPL) must be identical to, including the revisions listed, the enclosed labeling (text for the package insert, text for the patient package insert, immediate container labels for U.S. and Expanded Access for export). These revisions are terms of the NDA approval. Marketing the product before making the revisions, exactly as stated, in the product labeling may render the product misbranded and an unapproved new drug.

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this "**FPL for approved NDA 21-752.**" Approval of this submission by FDA is not required before the labeling is used.

Products approved under the accelerated approval regulations, 21 CRF 314.510, require further adequate and well-controlled studies to verify and describe clinical benefit. Since Viread® (tenofovir disoproxil fumarate) is currently approved under subpart H and confirmatory trials are ongoing, it is necessary to apply accelerated approval regulations to Truvada™ Tablets. We remind you of your post marketing study commitments in your approval letter for Viread® dated October 26, 2001, and the agreed upon amendment during a February 2, 2003 teleconference. This commitment, along with its expected completion date is listed below.

- Study GS-01-934, "A Phase III, Randomized, Open-Label, Multicenter Study of the Treatment of Antiretroviral-Naïve, HIV-1 Infected Subjects Comparing Tenofovir Disoproxil Fumarate and Emtricitabine in Combination with Efavirenz Versus Combivir (lamivudine/zidovudine) and Efavirenz". The letter of approval for VIREAD references Study GS-01-928 instead of study GS-01-934. However, on February 7, 2003, during a Gilead-FDA teleconference, the Agency agreed that Gilead substitute study GS-01-928 with study GS-01-934, as the second confirmatory trial to support traditional approval for VIREAD. The original protocol for study GS-01-934 was submitted to IND 52,849 (serial number 522) on July 2, 2003 and the study is ongoing under that IND. Submission of 48 week safety and efficacy data on all enrolled patients is expected on or before September 30, 2004.

Submit final study reports to the VIREAD NDA and a summary of the study reports to this NDA. For administrative purposes, all submissions relating to this postmarketing study commitment must be clearly designated **"Subpart H Postmarketing Study Commitments."**

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We are deferring submission of your pediatric studies for ages 0 to 18 years until pediatric studies for the individual products (emtricitabine, IND 53,971, NDA 21-500 and tenofovir DF, NDA 21-356) have been completed, at that time the Division will assess whether additional pediatric studies will be necessary for the fixed-dose combination product Truvada™.

Your deferred pediatric studies required under section 2 of the Pediatric Research Equity Act (PREA) are considered required postmarketing study commitments. The status of this postmarketing study shall be reported annually according to 21 CRF 314.81. This commitment is listed below.

Following submission of ongoing pediatric studies for emtricitabine (IND 53,971 and NDA 21-500), due on or before December 31, 2004, and tenofovir DF (IND 52,849 and NDA 21-356), due on or before November 1, 2004, please submit the following:

1. A request for a waiver or proposal to conduct pediatric studies under PREA of TRUVADA® for the treatment of HIV in pediatric patients ages 0 to 18 years of age.

Timeframe for submission = On or before March 31, 2007

Submit final study reports to the individual products INDs and NDAs and a summary of the study reports to this NDA. For administrative purposes, all submissions related to this pediatric postmarketing study commitment must be clearly designated "**Required Pediatric Study Commitments.**"

In addition, we note your following postmarketing study commitments, specified in your submission dated July 28, 2004, that are not a condition of the accelerated approval. These commitments are listed below:

1. Provide 48-week efficacy, safety and resistance data from completed studies (GS-03-934 and Abbott M02-418) in which emtricitabine/ tenofovir DF were or are being administered in combination or as Truvada Tablets.

   Final report submission = within two years from NDA approval date.

2. Evaluate the use of Truvada Tablets in patients with significant renal impairment, defined as CrCl <30 mL/min.

   Final report submission = within fifteen months from NDA approval date.

3. Conduct a stability study on alternate trade dress (light blue) emtricitabine/tenofovir DF tablets under long-term conditions (30°C/65% RH) as well as accelerated conditions (40°C/75% RH) and submit the data.

   Final report submission = within fifteen months from NDA approval date.

Submit clinical protocols to your IND for this product. Submit nonclinical and chemistry manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled **"Postmarketing Study Protocol", "Postmarketing Study Final Report", or "Postmarketing Study Correspondence."**

While the following is not a postmarketing commitment, please note:

The stability data presented supports use of both trade dress forms of Truvada in the ICH climatic zones I and II. To support use in Climatic Zones III and IV, in addition to the stability studies under long-term (30°C/65% RH) and accelerated conditions (40°C/75% RH), you will need to conduct a stress stability study on one batch of tablets that are stored for three months at 50°C/ambient humidity and at 25°C/80% RH conditions as recommended in the FDA/ICH Guidance for Industry document entitled *Q1F Stability Data Package for Registration Applications in Climatic Zones III and IV (June 2004).* This information may be submitted as a Prior Approval Supplement to the NDA.

As required by 21 CRF 314.550, submit all promotional materials at least 30 days before the intended time of initial distribution of labeling or initial publication of the advertisement. Send two copies of all promotional materials directly to:

Division of Drug Marketing, Advertising
And Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Jeff D. O'Neill, ACRN, Regulatory Health Project Manager, at (301) 827-2362.

Sincerely,

{See appended electronic signature page}

Debra Birnkrant, M.D.
Director
Division of Antiviral Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

Enclosures